REMARKS/ARGUMENTS

Responsive to the Final Office Action dated December 23, 2009, Claim 1 has been amended. Claims 1-8 and 11-18 therefore remain pending for prosecution with Claims 1 and 11 being independent. Declarations under 37 C.F.R. 1.132 executed by inventors of the present invention, Dr. Benjamin P. Warner (hereinafter "Warner") and Dr. George J. Havrilla (hereinafter "Havrilla"), were previously submitted.

I. Claim Objections

Claim 1 was objected to because a typographical error resulted in the phrase "at least one binder having chemically associated and nonradioactive element" missing the article "a" before "chemically associated." Applicant has amended Claim 1 accordingly and therefore requests withdrawal of this rejection.

II. Claim Rejections - 35 U.S.C. § 112

Claims 1-8 and 11-18 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, it was asserted that the previous amendments to Claims 1 and 11 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, it was asserted that the specification does not contain support for the limitation that the receptors are "binder-free." In particular, the Office Action asserts that, when the claim terminology "binder-free" is given its broadest reasonable interpretation, "receptors that are 'binder-free' would encompass not only those receptors that have not yet been bound to the

binder, but also receptors that are not bound to or in contact with any other type of biomolecule or material." The Office Action notes that "in all of the examples disclosed in the instant specification, the receptors provided were *bound to beads*." Therefore, the Office Action concludes that, because "all of the disclosed examples involved receptors that would reasonably be considered to be *bound* to a binder (beads) in this manner, rather than being 'binder-free,' the specification fails to convey evidence of possession of methods in which a plurality of *binder-free* receptors are exposed to binder. Consequently, implicit or inherent support is not apparent because the claim terminology can be interpreted in a manner that would rule out all of the disclosed embodiments."

Applicant respectfully traverses these assertions for all of the reasons previously submitted and reasserts that, while pending claims must be given their broadest reasonable interpretation, such an interpretation must be *consistent with the specification.* In the present application, the precise terminology "binder-free" does not need to literally appear in the description because its meaning is inherent from a reading of the specification as a whole and the meaning the Examiner has attributed to the term "binder" is unduly broad and not consistent with the specification. Nonetheless, in the interest of expediting prosecution, Applicant has amended the claims to delete the term "binder-free" thereby rendering this rejection moot.

III. Claim Rejections - 35 U.S.C. § 102

A. Rejection of Claims 1-8 and 11-18 over Goldin

Claims 1-8 and 11-18 were rejected under 35 U.S.C. 102(b) as being anticipated by Goldin et al. ("Quantitation of Antibody Binding to Cell Surface Antigens by X-ray Fluorescence Spectrometry," *Biochimica et Biophysica Acta*, 552 (1979), 120-128). For the

following reasons, Applicant respectfully requests reconsideration and withdrawal of this rejection.

The Office Action asserts that Goldin teaches "a method of detecting binding, comprising the steps of exposing a plurality of receptors (2,4-dinitrophenol hapten receptors attached to the surface of CHO cells) to at least one binder (ferritin-labeled antibody) in order to form a binder-receptor complex" and that "one could consider either the 2,4-dinitrophenol moiety alone to be the receptors or alternatively, the CHO cells together with the attached moiety as receptors." The Office Action further asserts that Applicant "specification does not disclose the terminology 'binder-free' or provide a specific or limiting definition thereof" and that "[w]hen this terminology is given its broadest interpretation, this can be interpreted as referring to the fact that the receptors are not initially bound to the binder, which describes the situation in Goldin et al. prior to expose of the hapten-bearing CHO cells to ferritin-labeled antibody." Further, it is asserted that the "ferritin-labeled antibody binder of Goldin et al. may be said to be 'chemically associated' with a nonradioactive element in that ferritin contains iron, which is detectable by X-ray fluorescence." Goldin is asserted to further teach "washing the cell-antibody complexes and arraying the complexes onto a substrate (electron microscope grids) and "[b]inding of the antibody to the cells is then detected by measuring the X-ray fluorescence due to the heavy element (iron) in the labeled-antibody/CHO cell complexes."

Applicant respectfully traverses the Office Action's assertions of anticipation and respectfully submits that Goldin fails to anticipate the present invention because Goldin does not disclose each and every limitation of the claims at issue. The attachment of a fluorescent tag to a chemical or receptor could result in a conformational change which has been known to affect the binding affinity of the chemical or receptor because the tagged surrogates are structurally

different from their untagged counterparts. The present invention is therefore concerned with the evaluating the binding properties of receptors and chemicals using the untagged chemical or receptor and not with a tagged surrogate. Goldin, on the other hand, uses a tagged surrogate, namely, CHO cells with attached radio-labeled 2,4-dinitrophenol haptens. These tagged receptors are then exposed to ferritin-labeled antibodies and the number of bound antibodies is compared to the number of attached haptens in order to determine the distribution of binding within the tagged CHO cell population. Applicant has amended the claims to more specifically define the receptors as being nonradioactive. Therefore, because Goldin fails to teach all of the elements of independent Claims 1 and 11 and the claims depending therefrom, Goldin cannot therefore anticipate the invention as claimed.

B. Rejection of Claims 1-5 and 11-15 over Sano

Claims 1-5 and 11-15 were rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,391,590 to Sano et al. as evidenced by Sigma-Aldrich *Product Information Sheet, Material Safety Data Sheet, and Safety Statements for Cadmium* Chloride (Catalog No. 28811) and U.S. Patent No. 5,665,865 to Lerner et al.. For the following reasons, Applicant respectfully requests reconsideration and withdrawal of this rejection.

The Office Action asserts that Sano teaches "methods of determining metal-binding activity of streptavidin-metallothionein chimeric protein, in which the receptors (i.e., chimeric proteins) are exposed to at least one potential binder, namely the metal ion Cd^{2+} which is provided as $CdCl_2$ during the course of protein purification." Sigma-Aldrich is then cited "as an evidentiary reference to show that the metal ion binder $Cd2^{+}$ as taught by Sano et al. is associated with an element that is nonradioactive." Finally, Lerner is cited "as an evidentiary reference to show that the metal ion binder $Cd2^{+}$ as taught by Sano et al. is a cofactor." Therefore, the Office

Action concludes that, "in light of the evidence of Sigma-Aldrich et al. and Lerner et al., the binder taught by Sano et al. is a member of the recited Markush groups of claims 1 and 11 and also has a chemically associated element which is non-radioactive."

It is further asserted that the reference "teaches spotting (i.e. arraying) the proteins onto a substrate (polypropylene membrane) . . . [wherein] the arrayed proteins were then subjected to quantitative X-ray fluorescence in order to determine the amount of metals in the sample spot." The Office Action states that "[t]his reads on the instantly claimed step of detecting an X-ray fluorescence signal generated by the detectable element, since the signal of the deposited protein-bound heavy metal ion (cadmium) is measured thereby." Furthermore, "[r]egarding the limitation that the receptor is 'unbound' and then arrayed in 'bound' form, the chimeric protein of Sano et al. would be considered to be initially unbound before it is contacted with the metal ion during dialysis. When the sample is then spotted onto a membrane after the dialysis step, protein bound to Cd^{2+} would be arrayed." It is concluded that "[b]y this process, unbound metal ion would be separated form [sic] bound and unbound receptor."

Applicant respectfully traverses the Office Action's assertions of anticipation and respectfully submits that Sano fails to anticipate the present invention because Sano does not disclose each and every limitation of the claims at issue. First, Sano's methods are directed toward the conjugation with or radioactive-labeling or tagging of biological material containing biotin with various heavy metal ions, their stable isotopes, or their radioisotopes. In the present application, Applicant's method requires exposing a binder-free receptor to a binder that includes a nonradioactive element detectable by X-ray fluorescence to form at least one bound receptor-binder complex as claimed in amended Claims 1 and 11. Sano, on the other hand, does not teach the detection of X-ray fluorescence from a bound receptor-binder complex. Sano also does not

teach the detection of X-ray fluorescence directly from a binder. Rather, Sano detects X-ray fluorescence from a radioactive tag. In other words, without the required tag, Sano would not be able to detect any X-ray fluorescence from the array or the binder. The Office Action itself supports this conclusion because "the metal ion Cd^{2+} which is provided as $CdCl_2$ during the course of protein purification" cited by the Office Action is, in fact, a radioactive label or tag. The Office Action asserts that that Sigma-Aldrich and Lerner teach that $CdCl_2$ is not radioactive and therefore show that the metal ion binder Cd^{2+} as taught by Sano is associated with an element that is nonradioactive. However, the Office Action misstates Applicant's claimed method in that the claimed binder must have "a chemically associated and nonradioactive element detectable by X-ray fluorescence" and, since it is the heavy metal ion Cd^{2+} that is the detectable element in Sano's method, the fact that it may be associated with another, different, nonradioactive element does not meet the terms of Applicant's claimed invention. In contrast, Applicant's claimed invention measures nonradioactive elements within the binder since it is the bound array members that are being detected by X-ray fluorescence and not a tag or label.

Sano is therefore nothing more than a part of the background for one of the unsolved needs in the art met by the present invention. As stated in Applicant's Background of the Invention, the attachment of a fluorescent tag to a chemical or receptor could result in a conformational change which has been known to affect the binding affinity of the chemical or receptor because the tagged surrogates are structurally different from their untagged counterparts. The present invention is therefore concerned with the evaluating the binding properties of receptors and chemicals using the untagged chemical or receptor and not with a tagged surrogate as disclosed by Sano. Therefore, because Sano fails to teach all of the elements

of independent Claims 1 and 11 and the claims depending therefrom, Sano cannot therefore anticipate the invention as claimed.

IV. Claim Rejections - 35 U.S.C. § 103

A. Obviousness

When determining the question of obviousness, underlying factual questions are presented which include (1) the scope and content of the prior art; (2) the level of ordinary skill in the art at the time of the invention; (3) objective evidence of nonobviousness; and (4) the differences between the prior art and the claimed subject matter. Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). Moreover, with regard to the last prong of the *Graham* inquiry, "[t]o determine whether there was an apparent reason to combine the known elements in the way a patent claims, it will often be necessary to look to interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the marketplace; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit." KSR International v. Teleflex Inc., 127 U.S. 1727 (2007).

Applicant does not contest that U.S. Patent No. 4,663,277 to Wang that has been cited and relied on by the Examiner has at least marginal pertinence to the particular problem(s) solved by the present invention in that the reference discloses a method for detecting viruses in which an extended solid phase coated with antiviral antibody is employed to bind and remove virions from a specimen by forming an immuno-complex with antigens of the virions. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 8781, 8786 (Fed. Cir. 1983).

The person of ordinary skill in the art is a hypothetical person who is presumed to know the relevant prior art. Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 962,

1 USPQ2d 1196, 1201 (Fed. Cir. 1986). The level of ordinary skill in the art of detecting binding events in a receptor-binder array may be determined by looking to the references of record. In re GPAC, Inc., 57 F.3d 1573, 35 USPQ2d 1116 (Fed. Cir. 1995). The references of record in this case reveal that a moderate level of sophistication in the chemical and biochemical arts is associated with one of ordinary skill. Thus, Applicant submits that, as substantiated by the cited references, those with at least a bachelor's degree in chemistry or biochemistry or the like would most likely be a person with ordinary skill in this field of endeavor.

With respect to objective evidence of nonobviousness, Applicant submits that the record supports the conclusion that there are long-felt but unsolved needs met by the present invention. The present invention is directed to the particular problem of providing a method for detecting binding events in order to assist in the identification of potentially important polymers, drugs, catalysts, and the like. However, prior art methods have required the attachment of a fluorescent tag to a potential binder in order to make the binder visible which may change the conformation of the binder. The present application is directed to a method of detecting binding events that does not use fluorescent or radioactive tags or labels in order to detect the binder. This feature represents a solution to long felt needs in the art that could not be met by the known prior art.

Finally, prima facie obviousness requires that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references. This motivation-suggestion-teaching test informs the Graham analysis. "To reach a non-hindsight driven conclusion as to whether a person having ordinary skill in the art at the time of the invention would have viewed the subject matter as a whole to have been obvious in view of multiple references," there must be "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is

correct." In re Kahn, (Fed. Cir. 2006). The *KSR International* decision by the Supreme Court has not eliminated the motivation-suggestion-teaching test to determine whether prior art references have been properly combined. Rather, in addition to the motivation-suggestion-teaching test, the Court discussed that combinations of known technology that are "expected" may not be patentable. Stated in the affirmative, therefore, combinations are nonobvious and patentable if unexpected. In the present application, no single prior art reference nor any combination thereof (legitimate or otherwise) meets the claimed limitations of Applicant's invention.

B. Rejection of Claims 1-8 and 11-18 over Wang

Claims 1-8, and 11-18 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 4,663,277 to Wang. For the following reasons, Applicant respectfully requests reconsideration and withdrawal of this rejection.

The Office Action asserts that Wang teaches "methods for detecting viruses and/or proteins, in which a plurality of viruses or proteins (i.e., receptors) in a specimen is exposed to an extended solid phase component (i.e., substrate) which is coated in at least one location with antiviral or antiprotein antibody." It is asserted that "[t]his step in which viruses in the sample are bound to the solid phase via the antiviral or antiprotein antibodies reads on the claimed step of 'arraying' the receptors on a substrate when given its broadest reasonable interpretation." Moreover, the Office Action asserts that Wang teaches "exposing the arrayed receptors to at least one potential binder, namely the same antibody coated onto a mobile solid phase of dispersed microspheres." "In one embodiment, the microspheres in the binder may be doped with metal elements so as to enable detection by X-ray fluorescence . . ." and "[d]etection of the X-ray fluorescence of the metal element labels in the microspheres indicates that binding between the

receptors and the solid phased antibody(ies) has occurred." Finally, it is asserted that Wang teaches "separating the solid phase substrate from the specimen and from unbound microspheres by washing."

The Office Action admits, however, that the teachings of Wang differ from the claimed invention in that the prior art methods involve first arraying the receptors on the extended solid phase, followed by contacting with the plurality of antibody-microsphere binders whereas the instant claims requires that the bound receptor (after exposure to binder) be arrayed onto the substrate. This difference in order, however, is asserted to be nothing more than routine expediency. Therefore, the Office Action concludes that it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention by first contacting the receptors of Wang with binder (antibody-coated microspheres), followed by arraying of bound receptor onto the solid phase support. Absent evidence of criticality, the selection of any order of performing process steps is prima facie obvious. Consequently, one of ordinary skill in the art would have found it obvious to select any order of contacting receptor, binder, and substrate out of the course of routine optimization.

Applicant respectfully traverses these assertions and respectfully submits that Wang does render the present invention obvious because Wang fails to teach or suggest each and every element of the invention as claimed. In particular, and as acknowledged by the Office Action itself, Wang involves *first* arraying the receptors on the extended solid phase *followed by* contacting with the plurality of antibody-microsphere binders. The claimed invention, on the other hand, requires that the receptors be exposed to the binders prior to being arrayed onto a substrate. It is asserted in the Office Action that "Applicant has not demonstrated criticality with regard to the order in which the receptors are contacted with binder and with the substrate."

However, as a matter of logic, immobilizing the receptor onto a substrate (e.g., glass microscope slides or on tacky dot plates) and then exposing the receptor to potential binders would prevent the receptor and the binder from actually binding since the receptor would necessarily be immobilized. The specification, directly and impliedly, also imposes this order on the method steps. Applicant therefore submits that Wang fails to disclose the exposing step followed by the arraying step as claimed by Applicant in independent Claims 1 and 11.

Moreover, the Office Action does not address the failure of Wang to teach untagged binders as recited in Applicant's Claim 11. It is well known in the art that tagging involves modifying the original chemical by attaching a "tag" (a chemical group that fluoresces when exposed to ultraviolet or visible light, for example) to all or a portion of the chemical. The Examiner has unnecessarily limited the definition of "untagged" to one example used in describing a particular reference. It is clear from the context of the present application and the general knowledge of those skilled in the art that the term "untagged" means elements that are chemically associated and that are intrinsically integral to the component being measured. In the present application, Applicant's method requires exposing a nonradioactive receptor to a binder that includes a chemically associated and nonradioactive element detectable by X-ray fluorescence to form at least one bound receptor-binder complex as claimed in Claim 1 and Claim 11. Wang, on the other hand, does not teach the detection of X-ray fluorescence from a bound receptor-binder complex. Wang also does not teach the detection of X-ray fluorescence directly from a binder. Rather, Wang detects X-ray fluorescence from a tag. In other words, without the required tag, Wang would not be able to detect any X-ray fluorescence from the array or the binder. *See previously submitted Declarations by Warner ¶ 8(ii) and Havrilla ¶ 8(ii).* This fact is further evidenced by the requirement that Wang's "microspheres can include

dye or fluorescent compounds for direct visual observation, or have metal elements or iron oxide doped or entrapped within in order to provide X-ray fluorescent or electromagnetic signals." Moreover, in order for the tags to remain chemically unassociated, Wang encloses the tag in latex or a similar coating. In contrast, Applicant's claimed invention measures elements that are chemically associated and that are intrinsically integral to the component being measured since it is the bound array members that are being detected by X-ray fluorescence and not a "chemically unassociated" tag or label. *See Warner ¶ 8(iii) and Havrilla ¶ 8(iii).*

In fact, Wang is nothing more than a part of the background for one of the unsolved needs in the art met by the present invention. As stated in Applicant's Background of the Invention, the attachment of a fluorescent tag to a chemical or receptor could result in a conformational change which has been known to affect the binding affinity of the chemical or receptor because the tagged surrogates are structurally different from their untagged counterparts. The present invention is therefore concerned with the evaluating the binding properties of receptors and chemicals using the untagged chemical or receptor and not with a tagged surrogate as disclosed by Wang.

Accordingly, Wang fails to teach or suggest the modification asserted by the Examiner. Further, Wang also fails to teach or suggest all of the elements of independent Claims 1 and 11 and no resultant method for detecting binding events could have been created from this reference that would meet the limitations of Claims 1 and 11. Even if such a combination were possible, the Examiner's combination would require a substantial reconstruction and redesign of the elements of Wang and would also change its principles of operation. Furthermore, one of ordinary skill in the art would not have arrived at Applicant's claimed invention because Applicant's invention would not be an "expected" result of the modification of the Wang

reference since this reference fails to meet all the limitations of the subject claim. Therefore, Applicant's independent Claims 1 and 11 and the claims depending therefrom are nonobvious.

V. Conclusion

Applicant respectfully submits the claims are in condition for formal allowance and such is courteously solicited. If any issue regarding the allowability of any of the pending claims in the present application could be readily resolved, or if other action could be taken to further advance this application such as an Examiner's amendment, or if the Examiner should have any questions regarding the present amendment, it is respectfully requested that the Examiner please telephone Applicant's undersigned attorney in this regard. Should any fees be necessitated by this response, the Commissioner is hereby authorized to deduct such fees from Deposit Account No. 11-0160.

Respectfully submitted,

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